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Transcranial direct current stimulation (tDCS) priming of 1 Hz repetitive transcranial magnetic stimulation (rTMS) modulates experimental pain thresholds

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HIGHLIGHTS

- Priming motor cortex with tDCS before 1 Hz rTMS standardizes its effects.
- This technique is applied to experimental pain thresholds.
- Cathodal tDCS – 1 Hz rTMS increased heat and cold pain thresholds.
- Anodal tDCS – 1 Hz rTMS decreased cold pain thresholds.
- tDCS priming may have applications in pain relief in the clinic.

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ABSTRACT

Transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) of primary motor cortex (M1) modulate cortical excitability. Both techniques have been demonstrated to modulate chronic pain and experimental pain thresholds, but with inconsistent effects. Preconditioning M1 with weak tDCS (1 mA) standardizes the effects of subsequent stimulation via rTMS on levels of cortical excitability. Here we examine whether 1 Hz rTMS, primed with tDCS, could effectively standardize the modulation of pain thresholds. Thermal pain thresholds were determined using quantitative sensory testing (QST) of the palmar thenar of both hands in 12 healthy males pre and post tDCS – 1 Hz rTMS over the hand area of the left M1. Cathodal tDCS preconditioning of 1 Hz rTMS successfully reversed the normal suppressive effect of low frequency rTMS and effectively modulated cold and heat pain thresholds. Conversely, anodal tDCS – 1 Hz rTMS led to a decrease in cold pain thresholds. Therefore, this study supports that preconditioning M1 using cathodal tDCS before subsequent stimulation via 1 Hz rTMS facilitates the production of analgesia.

1. Introduction

Pain is a global health problem that decreases patient quality of life. Due to the multiple different causes of pain, and the complexity of the pain network, it may be that alone, pharmacology will never provide adequate pain relief. Non-invasive cortical neurostimulation techniques offer an alternative or supplement to pharmacological interventions in pain relief, and are less costly than implanted stimulation [28]. Two major neurostimulation techniques: transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS), particularly of primary motor cortex (M1), have recently emerged as successful in the modulation of chronic and experimental pain [4,16]. Recent studies on the preconditioning effects of tDCS applied to M1 on subsequent rTMS suggest that this method may act to stabilize neural circuits and enable neurostimulation protocols appropriate for clinical applications. Here this preconditioning protocol is used to assess effectiveness in modulating experimental pain thresholds.

1.1. tDCS

tDCS is a neuromodulatory technique, where weak electrical current (~1 mA) is non-invasively applied to cortical targets. tDCS does not function to induce action potentials in the neurons, but rather to influence spontaneous neuronal activity already occurring in the brain in a polarity dependent fashion [15,17,27]. Anodal tDCS has been found to induce an increase in cortical excitability via the depolarisation of neuronal membrane potentials and

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cathodal tDCS has been shown to decrease cortical excitability via the hyperpolarisation of these [13]. Short lasting effects of tDCS on cortical excitability are mediated by the activity of sodium and calcium channels, whereas long term after effects depend on both changes in the membrane potential and modulations of the N-methyl-D-aspartate (NMDA) and gamma-amino-butyric-acid (GABA) receptor efficacy [13].

Previous studies using tDCS to modulate pain thresholds have shown effectiveness of both anodal [1] and cathodal [2] stimulation in increasing pain thresholds [16]. This may be due to tDCS being somewhat non-focal, as the electrodes used to deliver the modulatory current are large; different electrode montages; and heterogeneous patient groups in clinical studies. fMRI studies have revealed that tDCS not only affects the underlying cortex, but also provokes sustained and widespread changes in regional neuronal activity[7]. It remains to be determined how these distant areas are affected, but it is probably through interconnections between the principally stimulated area and these structures [9]. These findings make the optimum polarity for consistent pain threshold reduction difficult to establish [16].

1.2. rTMS

rTMS is a non-invasive neurostimulation technique that can be used to modulate cortical excitability to suppress or facilitate underlying cortical activity. Stimulation of M1 with low frequency rTMS (1 Hz or less) is associated with decreased cortical excitability, whereas higher frequencies (20–50 Hz) have been associated with an increase in excitability [14].

rTMS of M1 has proven efficacious in the treatment of chronic pain [16,19]. Further, high frequency rTMS of M1 in healthy populations show this technique can modulate experimental pain thresholds [16,26]. It is thought rTMS acts to modulate pathways from the insula and orbitofrontal cortex to the posterior thalamus in order to upregulate these pain thresholds [12]. The effects of high frequency rTMS on pain thresholds have been demonstrated to last up to eight days [11].

1.3. tDCS primed rTMS

Siebner et al., demonstrate that tDCS may be used to "prime" or "precondition" the brain before subsequent stimulation via rTMS so that baseline cortical excitability can be standardized [25]. Low frequency (1 Hz) rTMS applied on its own, normally results in an inhibition of cortical excitability in relation to the targeted brain area. Siebner et al., found that preconditioning with cathodal tDCS altered the expected suppressive effect and led to cortical excitation. Similarly, preconditioning with anodal tDCS [6] resulted in an overall cortical inhibition after subsequent stimulation using 1 Hz rTMS, again altering the expected effects. These findings are thought to be due to cortical homeostatic plasticity [3].

In our study the technique of tDCS primed 1 Hz rTMS is applied to experimental pain threshold modulation. The aim is to prime M1 using a preconditioning inhibitory session of cathodal tDCS, to cause an initial inhibition of cortical activity, reducing neuronal thresholds, thereby facilitating the overall increase in cortical excitability upon subsequent stimulation of low frequency rTMS. The prediction is that this increased cortical excitation will in turn, increase pain thresholds.

2. Materials and methods

2.1. Participants

Twelve healthy males (mean age, 21.5 years, 10 right handed); naïve to the experimental aims, participated in the study. No participants reported any previous or concomitant psychiatric or neurological disease, any conditions associated with acute or chronic pain or with somatosensory abnormalities. The study was performed in accordance with the Declaration of Helsinki and approved by the Faculty of Health Sciences Research Ethics Committee, Trinity College Dublin, Ireland.

2.2. Quantitative sensory testing (QST)

To determine thermal detection and pain thresholds, QST was performed using a TSA-2001 NeuroSensory Analyzer apparatus (Medoc, Ramat Yishai, Israel) that applied thermal stimuli and recorded participants' responses [6]. Standardized instructions provided with the TSA-2001 were given to each participant. The psychophysical method of limits was used to determine: cold sensation threshold (CS); warm sensation threshold (WS); cold pain threshold (CP) and heat pain threshold (HP). A 3 cm × 3 cm thermode was attached to the palmar thenar with a Velcro® strap, with thresholds determined for the hand both ipsilateral and contralateral to M1 stimulation. For CS and WS, the thermode decreased/increased in temperature (Min temp: −0 °C; Max temp: 50 °C) at a linear rate of 1 °C/s and a return rate of 1 °C/s with an adaptation temperature of 32 °C. The threshold for CS/WS was tested 4 times with an interval of 4–6 s between each separate, successive trial. The average value of the 4 trials was expressed in degrees centigrade (°C) and taken as the participant's detection threshold. In determining CP/HP thresholds, the thermode decreased/increased in temperature, but at a linear rate of 1.5 °C/s and return rate of 10 °C/s. These thresholds were measured over 3 successive trials with an interval of 10 s between each trial, before averaging. These threshold measurements were not counterbalanced; rather innocuous sensation perception threshold measurements (CS/WS) preceded pain perception thresholds (CP/HP) in order to avoid possible sensitivity changes caused by painful stimulation [5] (Fig. 1(a)).

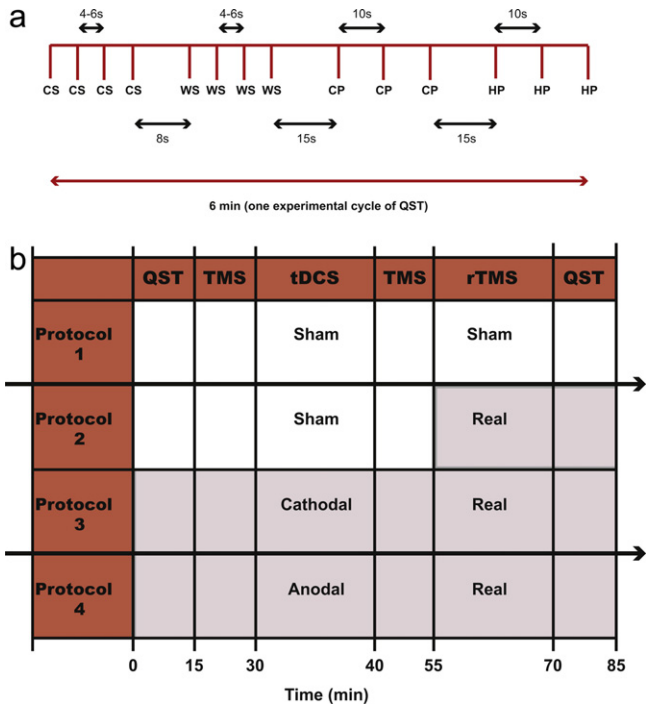

Fig. 1. (a) Timeline of one QST. QST was performed on both the ipsilateral and contralateral hand to the neurostimulation. (b) Timeline of neurostimulation protocols.